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Biointerfaces promoting tissue healing

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Cell adhesion to extracellular matrices plays central roles in development and the formation, maintenance and repair of numerous tissues, including bone, muscle, and cartilage[1]. Moreover, cell adhesion to adsorbed proteins and adhesive sequences engineered on surfaces is important to biomaterials, tissue engineering, and biotechnological applications[2,3]. Cell adhesion to extracellular matrix proteins is primarily mediated by the integrin family of adhesion receptors[4]. In addition to anchoring cells, supporting cell spreading and migration, integrins provide signals that direct cell survival, proliferation, and differentiation. Because of the critical importance of cell adhesion, biomimetic strategies have focused on generating surfaces that present short bioadhesive motifs, such as the integrin-binding motif arginine-glycine-aspartic acid (RGD) from fibronectin (FN), to promote cell adhesion. While these engineered supports promote adhesive activities *in vitro*, healing responses in *in vivo* models have been marginal. We hypothesize that these suboptimal responses to these peptide-tethered surfaces arise from reduced biological activity compared to the native ligand, lack of specificity among integrins, and inability to bind non-RGD integrins.

We have engineered biointerfaces that mimic the secondary and tertiary protein structure of fibronectin and type I collagen to convey integrin binding specificity. The fibronectin-mimetic ligand FNIII7-10 is a recombinant FN fragment that presents the PHSRN synergy and RGD sites in the correct structural context and exhibits high specificity for the $\alpha 2\beta 1$ integrin receptor. The collagen-mimetic ligand is a synthetic triple helical peptide containing the GFOGER binding motif and is selective for $\alpha 2\beta 1$ integrin. Bioadhesive surfaces were engineered on clinically relevant, commercially pure titanium supports. These surfaces directed integrin-specific adhesion, signalling, and osteoblastic differentiation compared to controls and reference materials (titanium) in primary bone marrow stromal cells. Importantly, these engineered surfaces enhanced osseointegration in terms of bone-implant contact and mechanical fixation for titanium implants in a cortical bone rat model. Moreover, FNIII7-10-functionalized titanium significantly improved functional implant osseointegration compared to RGD-functionalized and unmodified titanium *in vivo*. This work demonstrates that integrin binding specificity regulates healing responses to implanted biomaterials and identifies a strategy for the rational design of materials for regenerative medicine.

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